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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

008378

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MAY 28 1991
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MEMORANDUM

SUBJECT: Triclopyr Herbicide (Garlon 3A) - Evaluation of Additional Data on Subchronic and Chronic Toxicity/Carcinogenicity Studies; Reconsideration of the Registrant's Request for an Extension of the EUP (No. G2719-EUP-1)

Tox Chem No.: 883I
HED Project No.: 1-1268

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THRU: Marcia van Gemert, Ph.D., Branch Chief
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Registrant: DowElanco, Indianapolis, Indiana

Action Requested: Upon review of the additional data submitted by the registrant, determine if the toxicology data base for triclopyr can support extension of the EUP and temporary tolerances for fish, shellfish and potable water.

Recommendations: Base on the evaluation of the additional data submitted by the Registrant the 90-day feeding rat study, the chronic toxicity/carcinogenicity study in rats and the mouse carcinogenicity study are upgraded to Core-Minimum classification. As a result, the toxicology data base is now adequate to support the two-year extension of the EUP and temporary tolerances for Triclopyr (Garlon 3A, 44.4% ai) for fish, shellfish and potable water.

Background

Toxicology Branch II has recently (Memo of Y.M. Ioannou, dated 3-29-92) determined that the toxicology data base for triclopyr (Garlon 3A) was not adequate to support the renewal of an EUP and temporary tolerance for Garlon 3A, for fish, shellfish and potable water. Major data gaps included the rat chronic toxicity study which was reviewed earlier and found to be core-supplementary data. With the present submission, the Registrant provided the Agency with additional data on the rat chronic toxicity/carcinogenicity study, the rat 90-day feeding study, and the mouse carcinogenicity study.

Evaluation of Additional Data

A. 13-Week Dietary Toxicity Study in F 344 Rats: This study was classified as Core-Supplementary data based on the fact that the test article homogeneity and stability were not reported. The Registrant has recently submitted information indicating that Triclopyr was homogeneously mixed in the diet so that "top" samples were 99 to 100% of the target concentrations while "Bottom" samples were 100-103% of the target concentration. Stability data, supplied by the Registrant, also showed that Triclopyr was stable for at least 8 days at room temperature. The provided data on homogeneity and stability are considered acceptable and thus all deficiencies for this study are now resolved. This study is upgraded to Core Minimum Classification

B. 2-Year Dietary Chronic Toxicity-Oncogenicity Study in F 344 Rats: Both, the chronic toxicity portion and the carcinogenicity portion of this study were classified as Core-Supplementary due to a number of deficiencies as specified in the data evaluation report. The Registrant, in an effort to resolve these deficiencies, provided the Agency with additional data and/or explanations/justifications. Each of the deficiencies are listed below followed by the Registrant's response and the reviewer's comments:

1. Provide the Agency with Data pertaining to Triclopyr Stability.

   Data on the stability of Triclopyr indicate that when Triclopyr is mixed with the diet under room temperature is stable for at least 8 days with practically no loss of chemical due to degradation.
   This issue is considered resolved.

2. Provide the Agency with a list of clinical signs of toxicity with particular attention given to the urogenital tract.

The Registrant provided palpable mass data as well as the results of clinical observations throughout the study. These results indicate that there were no major signs of toxicity that could be attributed to treatment with Triclopyr. This issue is considered resolved.

3. Provide justification for using two animals/cage.

The Registrant's response to this issue appears to be acceptable and thus this issue is resolved.

4. Address the great variability observed in clinical chemistry individual values.

The Registrant attributed this variability to true differences in individual animals rather than to technical problems. Such variability is even more pronounced (according to the Registrant) when dealing with aged animals as is the case at the end of the 2-year rat study. Such animals usually have spontaneous tumors and/or other diseases which contribute greatly to the variability of clinical chemistry or other toxicologic parameters.

Although the Registrant's explanations for this variability appear to be reasonable, the variability observed in this study (mainly at terminal sacrifice) does not allow us to establish the effect of Triclopyr on some clinical chemistry parameters. For future projects the Registrant is urged to resolve methodology and/or technical problems before measuring clinical chemistry parameters. Although this issue is not completely resolved, we believe that the overall interpretation of the data in this study is not greatly affected by the variability in a few clinical chemistry values.

5. Carry out statistical analyses on all important data.

The Registrant provided the requested statistical analysis on major parameters for animals treated with Triclopyr up to 12 months. Because of great variability in data from the 2-year time point, such statistical analysis was not considered useful in interpreting the data. The provided statistical analysis on major parameters did not change the overall conclusions on this study.
This issue is considered resolved.

6. Address the major differences that exist between the 6-, 12- and 24-month study groups particularly pertaining to the incidence of renal tubule pigmentation.

Based on additional data submitted by the Registrant, the incidence of pigmentation in the proximal tubules at the 12-month sacrifice (Satellite Group) as it appears in the DER (Table 3), is incorrect as it reports the incidence of degeneration of proximal tubules, rather than pigmentation. The actual incidence of increased proximal tubule pigmentation should read: Males- 0/10, 0/10, 0/10, 0/10 for the control, low, mid and high dose groups, respectively. Females- 1/10, 1/10, 6/10, 10/10 for the control, low, mid and high dose groups, respectively.

Based on this correction, it appears that the increased, pigment in proximal tubules was consistently present in female rats especially at the high dose tested (36 mg/kg/day) at all time points examined. This issue is thus considered resolved.

7. Establish the nature of the pigment in the renal tubules and supply the Agency with historical control data.

The registrant provided the Agency with adequate information in trying to establish the nature of the pigment in renal tubules. This pigmentation appears to be the result of hemosiderin deposits as well as PAS-positive and PAS-negative lipofuscinlike granules in renal tubular epithelial cells. The presence of this pigment in rat kidneys has been documented by many investigators and, apparently, the increased pigment incidence seen with Triclopyr treatment, especially in the high dose females, does not represent an adverse effect. The limited historical control data supplied by the Registrant for rat kidney pigmentation, substantiates the Registrant's contentions that this renal pigment is of high occurrence in the rat and probably does not represent an adverse effect. Based on the historical control data submitted, the incidence of kidney tubular cell pigment was 74-96% in male and 90-92% in female F344 rats.
This issue is considered resolved.

Based on the results of this study the systemic NOEL=12 mg/kg/day and the LEL=36 mg/kg/day (based on statistically significant decrease in hemoglobin, hematocrit and red blood cell values and statistically significant increase in kidney relative and absolute weight).

Based on the results obtained from the 90-day feeding study in F344 rats with Triclopyr, the highest dose

tested in this study (2-year chronic/carcinogenicity), 36 mg/kg/day is acceptable as the MTD. In the 90-day feeding study degeneration of renal proxinal tubules was observed in the dose levels of 20, 50 or 250 mg/kg/day. Reduction in body weight gains was also seen at the 20 mg/kg/day dose in male rats.
Triclopyr was not carcinogenic in male or female F344 rats.
This study is upgraded to Core-Minimum classification for both, chronic toxicity and carcinogenicity. The carcinogenicity study satisfies guideline requirements only when taken together with this 90-day feeding study in rats (document # 005667; MRID #073873).

C. 22-Month Carcinogenicity Study in Mice

This study was classified as Core-Supplementary data in the original review due to a number of deficiencies. With this submission the registrant provided the Agency with additional data and/or justifications for the resolution of these deficiencies.

1. Provide the Agency with the 28-day preliminary range-finding study conducted in male and female mice.

   This study was requested in order to confirm that the dose levels for the mouse carcinogenicity study were appropriately selected. The submitted study demonstrates that the selection of the dose levels for the mouse carcinogenicity study (50,250 and 1250 ppm) was appropriate based on a number of toxic lesions observed at the dose levels of 1600 and 3200 ppm in the range finding study. Some toxic lesions (such as centrilobulur swelling and degeneration of hepatocytes), were also seen at the 800 ppm dose level. Although the MTD appears to have been approximated in the mouse carcinogenicity study (reduction in body weight gains by 10% in both sexes), the additional information from the range-finding study ends support to this effect.
   This deficiency is now considered resolved.

2. Explain why within groups there was a tremendous variation in body weight and clinical chemistry and hematology values.

   The Registrant's response to this issue is identical to the response given for variability seen in the rat chronic/carcinogenicity study discussed earlier (see section B4). According to the Registrant, such variability is very common especially in aging animals, as is the case with the terminal sacrifice in this

22-month mouse study. Indeed the results reported in this study indicate that invariably higher variability was seen at terminal sacrifice rather than at earlier time points such as at 6 or 12 month measurements. Although this high variability is of concern (possible loss of quality control) we agree with the Registrant that terminal clinical chemistry and hematology values do not contribute heavily towards the critical interpreta-tion of the results of this study. This issue is thus considered resolved.

This study is upgraded to Core-Minimum classification and satisfies guideline requirements (83-2) for a mouse carcinogenicity study.

Other Considerations

1. Bridging Studies

According to the Registrant, Garlon 3A (44.4% ai as the triethylamine salt) is considered to be the technical grade of Triclopyr. However, except for the acute toxicity studies, all other studies were conducted with the acid form of Triclopyr with 98% purity (3,5,6-trichloro-2-pyridinyloxyacetic acid). The Registrant contends that GArlon 3A (triethylamine salt) undergoes a very rapid hydrolysis (in vivo) to generate the acid form of Triclopyr. (Hydrolysis studies were apparently submitted to the Agency by the Registrant). In view of the above, the Agency will consider requesting (during phase IV of reregistration) "bridging" studies on Garlon 3A so that it can be determined whether or not the triethylamine salt and the acid form of Triclopyr are toxicologically equivalent.

2. Acute Toxicity Studies

Acute toxicity studies were conducted with Garlon 3A, 44.4%, triethylamine salt of Triclopyr. All studies were reviewed and found to be acceptable. Review of the eye irritation study indicates that Garlon 3A is a severe eye irritant (Toxicity Category I); thus, the label should be amended, if necessary, to reflect this danger.

Acute toxicity studies conducted with the ethyl ester of Triclopyr (ethyl-3,5,6-trichloro-2-pyridyloxyacetate; 99% ai) were also submitted by the Registrant. A cursory review of these studies indicates that the ethyl ester form of Triclopyr is less toxic than the triethylamine salt.

Recommendations

Based on the Additional data submitted by the Registrant, the 90-day feeding study in rats, the 2-year chronic/ carcinogenicity study in rats and the mouse carcinogenicity study have been upgraded to Core-Minimum classification and they satisfy the guideline requirements. Thus, at present the data base for Triclopyr is adequate to support extension of the EUP and temporary tolerances for fish, shellfish and potable water for use of Garlon 3A to control woody, plant and perennial weeds in streams, rivers, ponds, lakes and other sites.

Toxicology Profile for Triclopyr

A. Data Requirements

Triethylamine Salt (Garlon 3A; 44.4% ai)	Required	Submitted	Core-Classification
81-1 Acute Oral Toxicity	Y	Y	Minimum
81-2 Acute Dermal Toxicity	Y	Y	Minimum
81-3 Acute Inhalation Toxicity	Y	Y	Minimum
81-4 Primary Eye Irritation	Y	Y	Minimum
81-5 Primary Dermal Irritation	Y	Y	Minimum
81-6 Dermal Sensitization	Y	Y	Guideline
Acid Form of Triclopyr (98% ai)			
82-1 Subchronic Oral (Rodent)	Y	Y	Minimum
82-1 Subchronic Oral (Nonrodent)	Y	Y	Supplementary[1]
83-1 Chronic Toxicity (Rodent)	Y	Y	Minimum
83-1 Chronic Toxicity (Nonrodent)	Y	Y	Not reviewed
83-3 Developmental Toxicity (rat)	Y	Y	Minimum
83-3 Developmental Toxicity (rabbit)	Y	Y	Minimum
83-4 Reproduction (rat)	Y	Y	Minimum
84-2 Mutagenicity - Gene Mutation	Y	Y	Acceptable
84-2 Mutagenicity - Str. Chrom. Aber.	Y	Y	Acceptable
84-4 Mutagenicity - Other Genotoxic Effects	Y	Y	Acceptable

[1]This requirement is satisfied by an acceptable 6-month dog feeding study.

B. Toxicology Issues

1. Reference Dose (RFD)

The current RFD for Triclopyr is set at 0.025 mg/kg/day based on a 6-month dog study with a NOEL of 2.5 mg/kg/day and a safety factor of 100. this RFD value has not been reviewed by the HED RFD committee and not verified by other Agency RFD committees due to data gaps existing in the Triclopyr Toxicology data base.

2. Pending Regulatory Actions

The Toxicology Branch is not aware of any pending regulatory actions against this pesticide.